# Abdominal adipose tissue distribution assessed by computed tomography and mortality in hospitalised patients with COVID-19

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# Abstract

### Background & Aims:

Visceral adiposity has been associated with an increased risk of critical illness in COVID-19 patients. However, if it also associates to a poor survival is still not well established. The aim of the study was to assess the relationship between abdominal fat distribution and COVID-19 mortality.

### Methods

In this six-month longitudinal cohort study, abdominal visceral (VAT) and subcutaneous adipose tissues (SAT) were measured by computed tomography in a cohort of 174 patients admitted to the emergency department with a diagnosis of COVID-19, during the first wave of pandemic. The primary exposure and outcome measures were VAT and SAT at hospital admission, and death at 30 and 180 days, respectively.

### Results

overall survival was not different according to VAT ($p = 0.94$), SAT ($p = 0.32$) and VAT/SAT ratio ($p = 0.64$). However, patients in the lowest SAT quartile (thickness lower than 11.3 mm ) had a significantly reduced survival compared to those with thicker SAT (77% vs 94% at day 30; 74% vs 91% at day 180, $p = 0.01$). Similarly, a thinner SAT was associated with lower survival in Intensive Care Unit (ICU) admitted patients, independently of sex or age ($p = 0.02$). The VAT/SAT ratio showed a non-linear increased risk of ICU admission, which plateaued out and tended for inversion at values greater than 1.9 ($p = 0.001$), although was not associated with increased mortality rate.

### Conclusions

In our cohort, visceral adiposity did not increase mortality in patients with COVID-19, but low SAT may be associated with poor survival.


# Introduction

The coronavirus disease 2019 (COVID-19) caused by SARS-CoV2, was declared a pandemic by the WHO on March 11, 2020 and still represents one of the main worldwide public health threat.

Hospital admission rates for patients with COVID-19 mainly depend on demographic characteristics such as age, gender and race. Nevertheless, it has been also estimated that obesity, defined as a body mass index (BMI) $\geq$ 30 Kg/m$^2$, is able to triplicate the risk of hospitalization due to COVID-19 infection [1].

Data from over 17 million primary care records showed that BMI raises the risk of death in COVID-19 patients, ranging from a 40% increase in subjects with a BMI between 35 to 40, to 90% in those with a BMI over 40 [2]. Obesity may represent a risk factor associated with a higher mortality rate independently

from other chronic comorbidities [3]. Hence, fat accumulation may be representative of disease severity and be linked to poor clinical outcomes.

However, recent work suggests that BMI does not accurately reflect adipose tissue mass in adults as it is not able to reflect body mass distribution and does not discriminate between fat and lean body mass [4, 5].

Visceral adipose tissue (VAT) is known to be more metabolically active compared to subcutaneous adipose tissue (SAT) and it is associated with low-grade inflammation, adipokines and pro-inflammatory cytokines production [6]. VAT accumulation leads to increased interleukin-6 (IL-6), tumor necrosis factor (TNF)-alpha and macrophage infiltration [7]. Elevated serum IL-6 and other pro-inflammatory cytokines are also hallmarks of systemic inflammation of COVID-19, which is known to be linked to disease severity and fatality [1]. Therefore, an excess of VAT may further exacerbate the pro-inflammatory status in COVID-19 patients.

Conversely, SAT is associated with lower systemic inflammation; lower risk of developing cardiometabolic diseases [8] and it has been reported being an independent predictor of survival [9, 10].

We previously showed that COVID-19 subjects with active lung disease admitted to the intensive care unit (ICU) had greater VAT and lower SAT than subjects not requiring intensive care [11]. However, whether such risk translates into decreased survival has not been fully established. The aim of this study is to evaluate the relationship between abdominal fat distribution and COVID-19 mortality. We hypothesized that excess VAT and lower SAT are associated with higher COVID-19 mortality.

# Materials and Methods

This was a single center longitudinal cohort study including patients admitted to the Emergency Department (ED) of Trauma Center Public Hospital Bufalini, Cesena, Italy, during the first pandemic wave from March 07, 2020 to April 28, 2020 for clinical suspicion of SARS-CoV-2 infection who underwent a thorax CT scan. During that timeframe, CT scans were performed in a total of 501 patients together with clinical evaluation and real-time reverse-transcriptase polymerase chain reaction (RT-PCR) from a nasal and/or throat swab. A diagnosis of confirmed COVID-19 was performed based on a SARS-CoV-2 positive RT-PCR together with signs, symptoms, and radiological findings suggestive of COVID-19. All patients with interstitial involvement and a positive COVID-19 test were diagnosed as having COVID-19 pneumonia.

Assessment of upper abdominal SAT and VAT were obtained using sagittal image from high resolution (HR) CT (Philips Diamon Select Brillance 64-slice CT), which was performed at admission to the ED and acquired by covering all thorax and upper abdomen region until a plane transverse to L2-L3, depending on lower diaphragm insertion, as previously described [11]. SAT was defined as the greatest thickness between the abdominal muscle wall and the skin-fat interface. VAT was defined as the greatest distance

between the anterior liver surface and the inner muscular wall (intra-reader agreement by Cohen's *Kappa* > 0.98 for both) [11].

The primary endpoint were indices of fat distribution (VAT, SAT and VAT/SAT ratio) at hospital admission and survival at 30 and 180 days from admission, respectively. The secondary outcome was ICU admission rate. Survival was analyzed using Kaplan-Meier curves with log-rank test comparing quartiles of VAT, SAT, and VAT/SAT ratio and Cox-regression models with fat modeled using a restricted cubic spline to allow for a non-linear relationship. Poisson regression models with fat modeled using a restricted cubic spline were used to analyze ICU admissions. VAT, SAT and VAT/SAT ratio was adjusted for gender and age through the Cox regression model. Continuous data were reported as median with range; categorical data were reported as number of observations (percentage). Statistical analyses were performed in R Statistical Software 3.3 (R Foundation for Statistical Computing, Vienna, Austria). All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki. This study was approved by the CEROM (Comitato Etico della Romagna) Ethical Committee with number Prot. 8654/2020.

# Results

Among 239 patients with a positive test for RT-PCR SARS-CoV-2, complete fat measurements and survival data were available in 174 patients. Of these patients, 140 (80%) presented CT features of interstitial pneumonia (COVID-19 pneumonia) and were thus included in the final analysis.

Forty-six patients (46/140; 33%) required ICU admission, 14 of them (10%) died within 30 days, and 5 (4%) died within 180 days from ICU admission. The most important and available characteristics of patients are reported in Table 1. The median BMI was 26.2 Kg/$m^2$ (range 18.4–51.9) Kg/$m^2$. The majority of patients were male (n = 85, 61%) and the median age was 61 (range 17–95) years old. The median value of VAT and SAT were 15 (range 2–38) mm and 16 (2–52) mm, respectively. The median VAT/SAT ratio was 0.80 (0.17–5.75). According to gender, the median VAT/SAT ratio, VAT and SAT were 0.71 (range 0.17–3.29), 14 (range 4–26) mm and 20 (range 2–45) mm in female patients; it was 0.91 (range 0.17–5.75), 15 (range 2–38) mm and 15 (range 2–52) mm in males.

Table 1
**Clinical and biochemical features of COVID-19 patients.**

| Characteristic | Value |
|---|---|
| Median age, range (years) | 61 (17–95) |
| Gender, n (%) | 85 (61%) |
| Male | 55 (39%) |
| Female | |
| ICU hospitalization, n (%) | 46 (33%) |
| VAT, mm, median (range) | 15 (2–38) |
| SAT, mm, median (range) | 16 (2–52) |
| VAT/SAT, mm, median (range) | 0.80 (0.17–5.75) |
| BMI, Kg/$m^2$, median (range) | 26.2 (18.4–51.9) |
| LDH, U/l, median (range) | 295 (154–888) |
| Lactate, mmol/l, median (range) | 1.04 (0.53–4.51) |
| Creatinine, mg/dl, median (range) | 0.84 (0.24–2.34) |
| eGFR, ml/min/1.73 $m^2$ median (range) | 91 (30–120) |
| Leucocytes, x$10^3$/mcl | 5.6 (2.4–16.5) |

VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; LDH, lactate dehydrogenase.

In the overall cohort, fat distribution was similar between COVID-19 patients who died compared to those who did not (VAT: 15.3 ± 8.3 mm versus 14.7 ± 7.0 mm, $p = 0.78$; SAT: 15.2 ± 8.1 mm versus 17.9 ± 8.8 mm, $p = 0.08$; VAT/SAT 1.25 ± 1.04 versus 1.07 ± 0.86, $p = 0.36$; respectively).

The overall survival was not different according to VAT ($p = 0.94$), SAT ($p = 0.32$) and VAT/SAT ratio ($p = 0.64$). When dividing in quartiles, we observed that patients who had the lowest SAT (SAT ≤ 11.25 mm) had a reduced survival compared to patients with a SAT higher than 11.25 mm (77% versus 94% at day 30, $p = 0.01$; 74% versus 91% at day 180, $p = 0.01$). By contrast, the overall survival remained unrelated to VAT ($p = 0.21$) or VAT/SAT ratio ($p = 0.45$) when looking at quartiles (Fig. 1a-c). These findings were also confirmed among patients admitted to ICU, where we observed that a thinner SAT was associated with lower survival, independently of gender or age ($p = 0.02$), while VAT or VAT/SAT ratio were not associated with overall survival.

Although it was not associated with survival, VAT/SAT ratio showed a non-linear increased risk of ICU admission, which plateaued out and tended for inversion at VAT/SAT > 1.9, independent of age and sex ($p = 0.001$). A similar non-linear increased risk of ICU admission was observed for VAT (Fig. 2). Supplementary table 1 summarizes the average relative risk (RR) per each 0.1 increase in VAT/SAT ratio.

Furthermore, we found that fat distribution was not related to in-hospital length of stay among survivors ($-0.008 < r < 0.187$; $p > 0.40$) but was associated with clinical and biochemical indices of disease severity. Indeed, VAT correlated inversely with leukocyte count ($r=-0.204$; $p = 0.03$) and the positive end-expiratory pressure (PEEP) ($r=-0.766$; $p = 0.004$), and directly with serum Interleukin-6 ($r = 0.709$; $p = 0.007$). SAT was inversely related with the qSOFA score ($r=-0.213$; $p = 0.043$) and circulating lactates ($r=-0.369$; $p = 0.034$), confirming an inverse association with disease severity.

# Discussion

In this study, we found that visceral adiposity does not increase mortality in a large cohort of COVID-19 patients, despite increasing the risk of intensive treatment. Furthermore, SAT thickness in the lowest quartiles may be linked to reduced survival in patients diagnosed with COVID-19 pneumonia.

Lack of association between visceral adiposity with mortality, and the potential protective effect of SAT, might be explained by a combination of mechanisms. First, adipose tissue primarily works as a source of body fat storage and therefore may provide a survival advantage during periods of starving or reduced calories intake associated with severe disease [7]. Second, SAT produces more favourable anti-inflammatory adipokines, such as adiponectin, which can control the inflammatory response and cardiometabolic risk, both factors associated with a poorer COVID-19 outcome [7]. By contrast, visceral adiposity did not impact on survival but it allowed for a non-linear increased risk of critical illness (ICU admission), which reached a plateau above a certain VAT or VAT/SAT threshold. This loss of linearity may reflect a simple “saturation effect” in proinflammatory cytokines produced from VAT or it may be due to the increased availability of fat storage. The latter would counterbalance the detrimental effect of visceral adiposity on the immune response.

Several studies have reported that, over a certain threshold, the damaging effects of a high VAT/SAT ratio or adiposity either reach a plateau or evens out. A phenomenon deemed “the obesity paradox” suggests that although obesity has been related to an increased risk of severe disease and illness, it may not always impact on survival. This phenomenon has been seen in coronary artery disease, kidney failure, pneumoniae and acute respiratory distress syndrome [12–14].

Other studies have reported mixed results ranging from no association [15–18] to a positive association [19–21] between visceral adiposity and mortality (reviewed in [22]).

For example, a report on Chinese patients, assessing the effect of VAT/SAT on survival as main outcome, found that visceral adiposity was not significantly associated with mortality ($p = 0.056$) although SAT alone was not assessed [16]. Our data are also consistent with another report from a large Italian population, which showed no association between COVID-19 mortality and VAT, or total abdominal adipose tissue [15]. Conversely, a more recent report found that higher VAT/SAT ratio was associated with 30-day mortality in hospitalised COVID-19 patients from Germany and Turkey (OR = 2.147, 95%CI 1.022 to 4.512; $p = 0.044$) [21]; Beltrao et al. also found that VAT > 150 $cm^2$ was an independent predictor of mortality in a Brazilian cohort of moderate-to-severe COVID-19 patients. Our data are also consistent with the study by Sheffler et al. who found that higher subcutaneous fat area had a protective effect against mortality in octogenarians COVID-19 patients [17].

Our study has limitations and strengths. We were not able to obtain a total abdomen scan. Furthermore, our data might not be generalized to other COVID-19 cohorts as clinical algorithms applied for ICU admission and ICU capacity may change according to centres. Due to the retrospective nature of the study with limited available data, we were not able to collect other clinical characteristics for a sufficient number of patients, and the missing data prevent us performing further analyses. Nevertheless, we were able to adjust for sex and age and we demonstrated no statistical significant differences in this setting.

To our knowledge, this is one of the largest studies, with the longest follow-up, examining the association between fat distribution and COVID-19 outcomes. We are also the first group to show that the association between Visceral adiposity and ICU is not linear. The use of routinely performed chest CT for measuring upper abdominal fat distribution, without the need for additional or repeated *ad-hoc* imaging is an advantage in our study. SAT appears to hold a prognostic value over VAT, by providing survival benefit in those with a more severe disease.

# Conclusion

Despite increasing the need of intensive treatment, visceral adiposity was not associated with mortality in our cohort of patients with COVID-19. Furthermore, a lower SAT may be associated with poor overall survival in COVID19 patients, including those admitted to ICU. Further research is needed to determine if measurement of VAT and SAT could improve risk assessment among individuals with COVID19.

# Declarations

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**Author contributions:** SB conceived the study, collected the data, contributed to the interpretation of the data and the writing of the manuscript. CP analysed the data, contribute to the interpretation of the data and the writing of the manuscript. AP and MG contributed to the interpretation of the data and the writing of the manuscript. ER contribute to data analysis. VA, EP and EG contribute to data collection. VA, NN and MM contribute to data interpretation. RS, FT and GA wrote the first draft, contributed to the interpretation of the data, and to the data analysis. All authors critically revised the manuscript for intellectual content. All authors have seen and approved the final draft. SB and RS are the guarantors of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Research data:** data will be shared upon reasonable request.

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# Figures

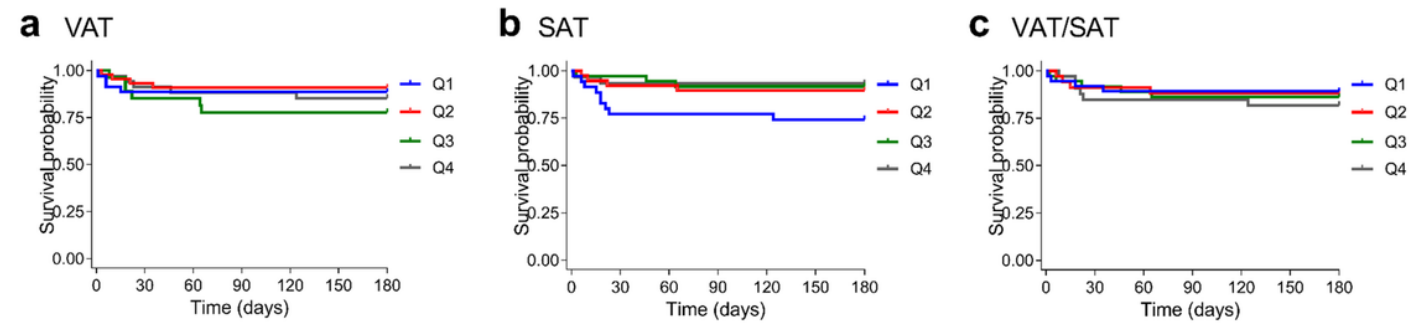


**Figure 1**

**Survival analyses according to indices of abdominal fat distribution.**The figures show survival at day 180 according to quartiles of VAT (**a**), SAT (**b**) or VAT/SAT ratio (**c**), in the COVID-19 patients with pneumonia. Patients in the lowest SAT quartile (SAT≤11.25 mm) had reduced survival compared to patients in the other quartiles (77% vs 94% at day 30; 74% vs 91% at day 180, *p*=0.01). By contrast, the overall survival remained unrelated to VAT (*p*=0.21) or VAT/SAT ratio (*p*=0.45)

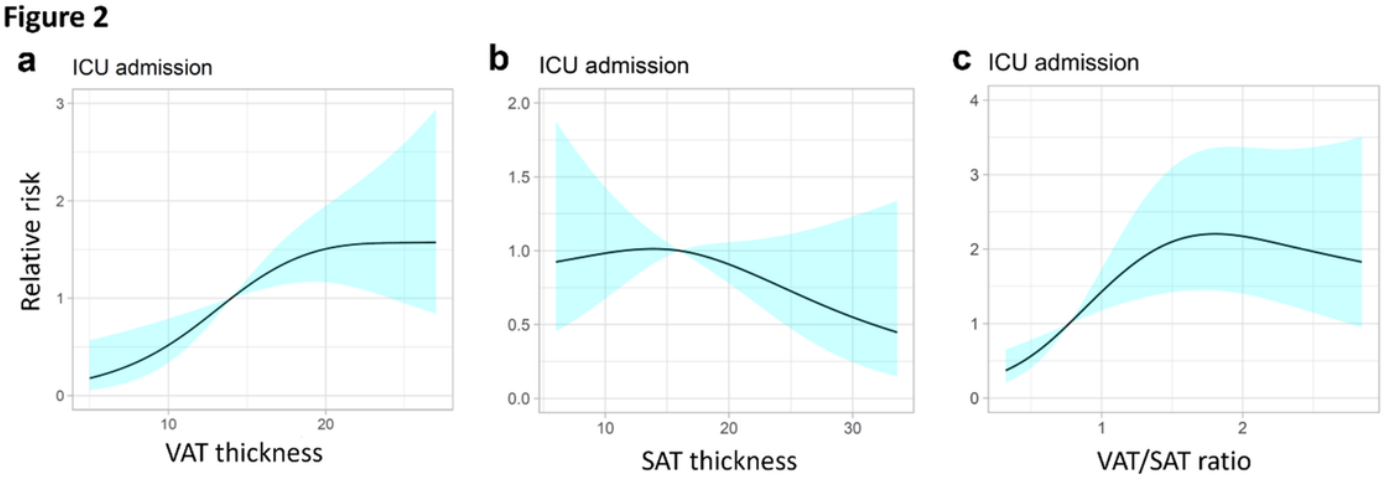


**Figure 2**

**Association between indices of abdominal fat distribution and ICU admission in COVID-19 patients.** The figure shows the association of VAT (**a**), SAT (**b**) and VAT/SAT ratio (**c**) with the risk of ICU admission. Although unrelated with mortality, VAT and VAT/SAT showed a non-linear increased risk of ICU admission, which plateaued out and tended for inversion at values of VAT/SAT greater than 1.9 (*p*=0.001).

# Supplementary Files

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- Supplementarymaterial.docx